Antibiotics dosing in patients with abnormal kidney function

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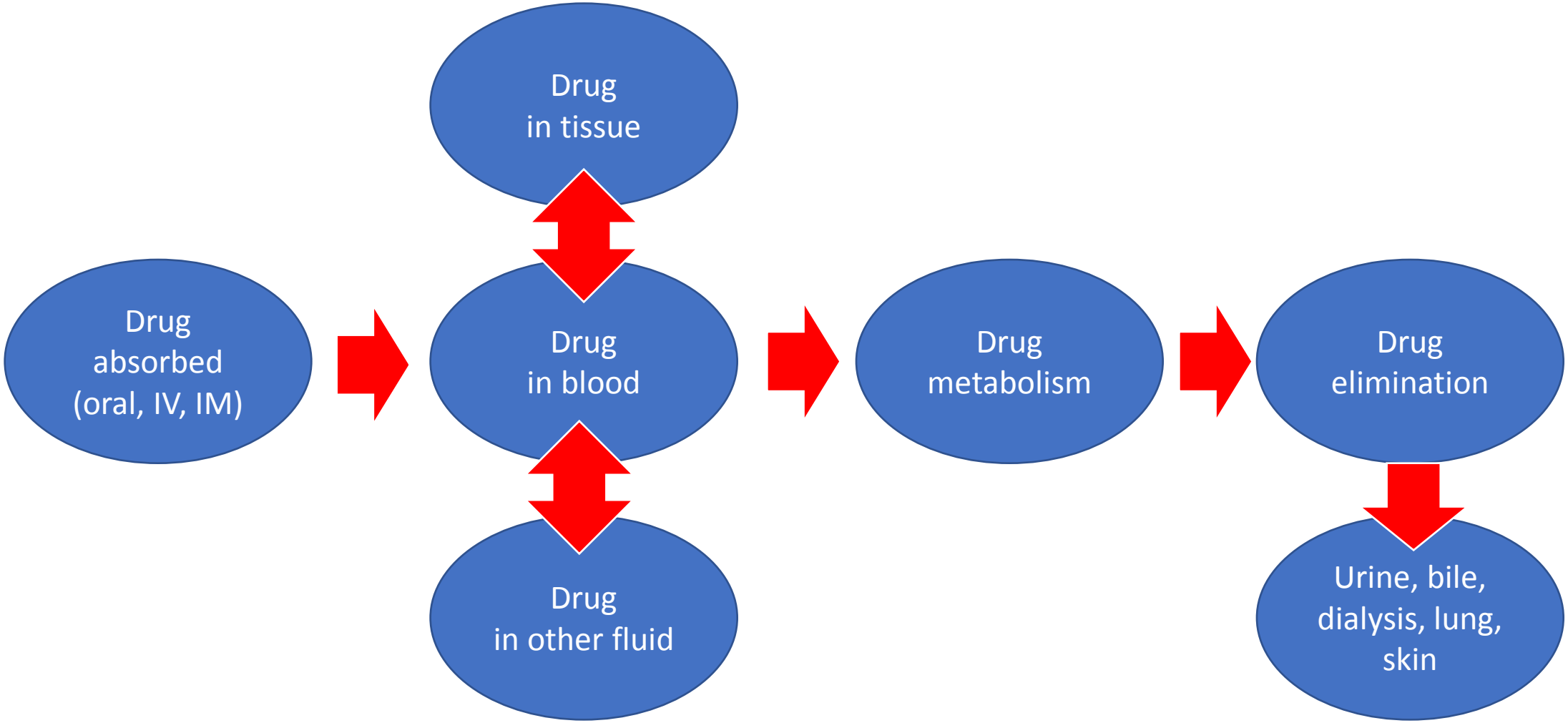
Area of interest

- The impacts of abnormal kidney function on pharmacokinetics of antibiotic
- How to modify antibiotic dose in patients with abnormal kidney function? Is “open-book” enough?
- What are factors to be concerned?

What are the common issues related to antibiotic administration in patients with abnormal kidney function?

- **Inappropriate dosing leading to toxicity**
  - overdosage: excessive accumulation of drug and its metabolites
- **ineffective therapy**
  - underdosage: overcautious or inappropriate dose adjustment

Basic pharmacokinetics

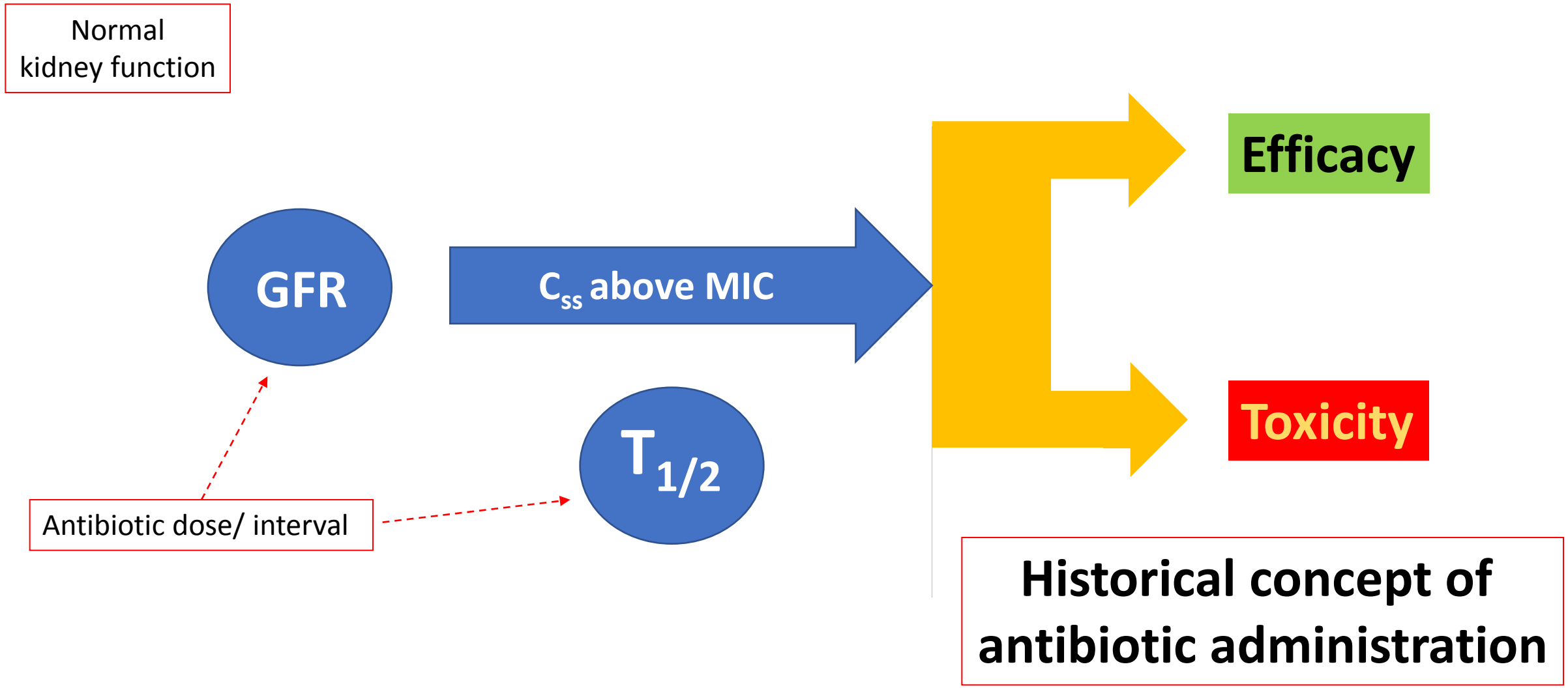


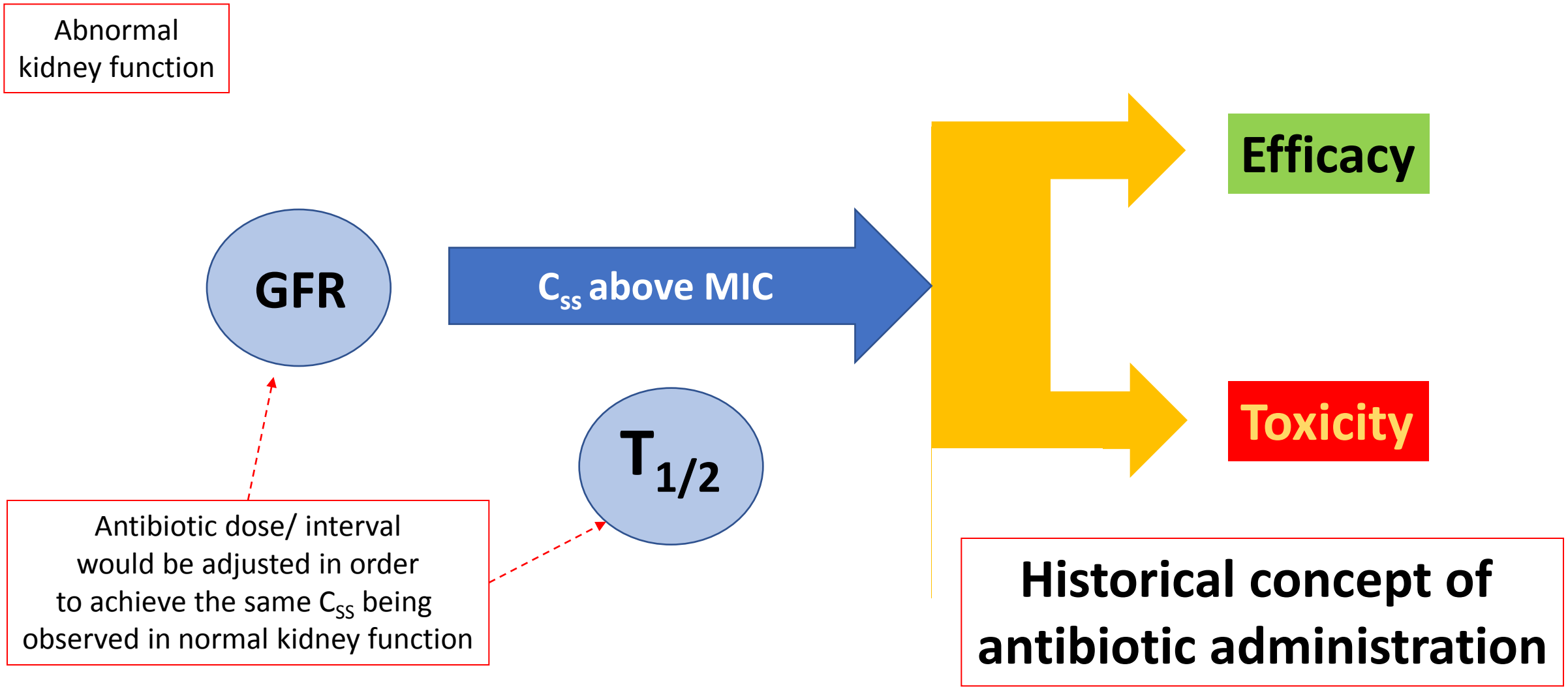
Effect of kidney diseases on various phases of PKs

Phase	Effect of renal diseases	Example
Elimination	**Reduced GFR** results in prolonged free drug eliminationT½ -Drugs that are highly protein bound are not filtered, but **actively secreted** into the proximal convoluted tubule -**Passive reabsorption** occurs at distal nephron	Drugs affected by reduced active secretion: - Ampicillin - Penicillin G - Trimethoprim

Effect of kidney diseases on various phases of PKs

Phase	Effect of renal diseases	Example	Phase	Effect of renal diseases	Example	Phase	Effect of renal diseases	Example
Absorption	**Gastroparesis and reduced peristalsis**: results in delayed gastric emptying and **prolongs the time to C_{max}.** **Alkaline environment (oral cavity & stomach) and drug interactions (e.g. PO_4 binders)** : reduces the absorption of many medications	- Tetracycline, - Oral FQs	**Distribution**	**Changes in V_d** in patients with renal dysfunction, i.e. increased V_d >>> need a loading dose. **Hypoalbuminemia** (decreased V_d in muscle- wasted person) >>> an increase in the free drug fraction of medications that are highly bound to albumin.	- β- lactams: loading dose once increased V_d - Higher free drug levels with decreased albumin: Penicillins, cephalosporins - Increased protein binding in CKD: Vancomycin	**Metabolism**	**Hepatic metabolism** of medications is inhibited in both CKD and AKI. -significantly slows both phase I and phase II reactions>reduces P-glycoprotein activity, resulting in increased bioavailability of some medications. **ESRD:** impaired renal epithelial metabolism	- Isoniazid


Normal kidney function
GFR
C_{ss} above MIC
$T_{1/2}$
Antibiotic dose/ interval
Efficacy
Toxicity
Historical concept of antibiotic administration


Abnormal kidney function
GFR
C_{ss} above MIC
$T_{1/2}$
Efficacy
Toxicity
Antibiotic dose/ interval would be adjusted in order to achieve the same C_{SS} being observed in normal kidney function
Historical concept of antibiotic administration

How to adjust the dose of antibiotic in patients with abnormal kidney function?

- Package insert
- Search engine
- Standard textbook

Mostly based on estimated GFR

Czock D, et al. Int J Clin Pharm. 2015;37(5):906-16.
Keller F, et al. World J Nephrol 2015;6; 4(3): 330-44.

Abnormal kidney function: Conditions to be concerned

- Acute kidney injury (AKI)
- Chronic kidney disease (CKD)
- AKI on top CKD
- The above conditions with varies types of RRT

Renal clearance determination : Conditions to be concerned

Unreliable estimated GFR

- Unstable kidney function: AKI and AKI on top CKD >>> critically ill individual
- Extreme over- or underweight (muscle mass)
- Extreme age group i.e. elderly
- Sex
- The effect of individual RRT

Usually over-estimated GFR

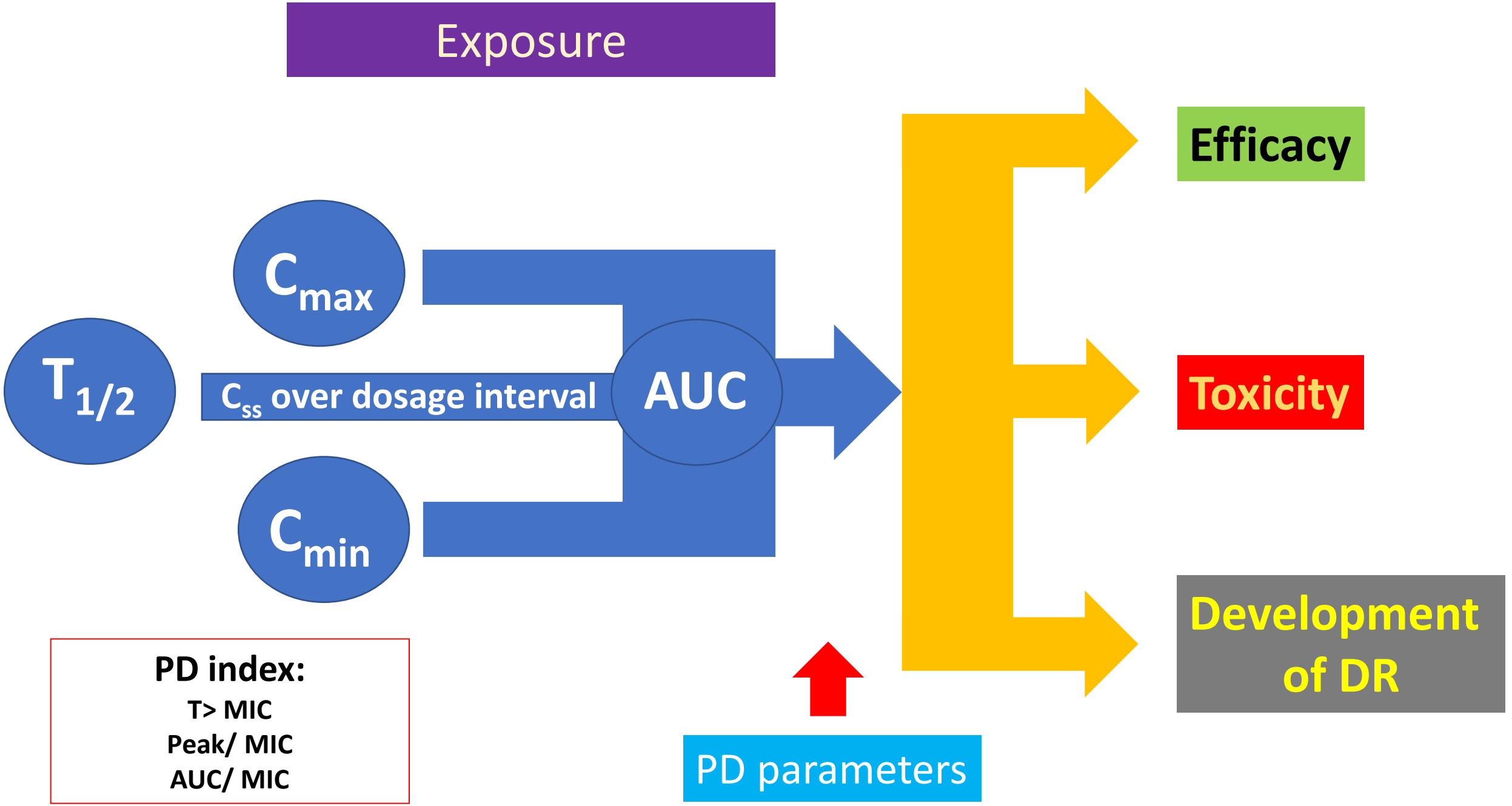
Usually under-estimated GFR

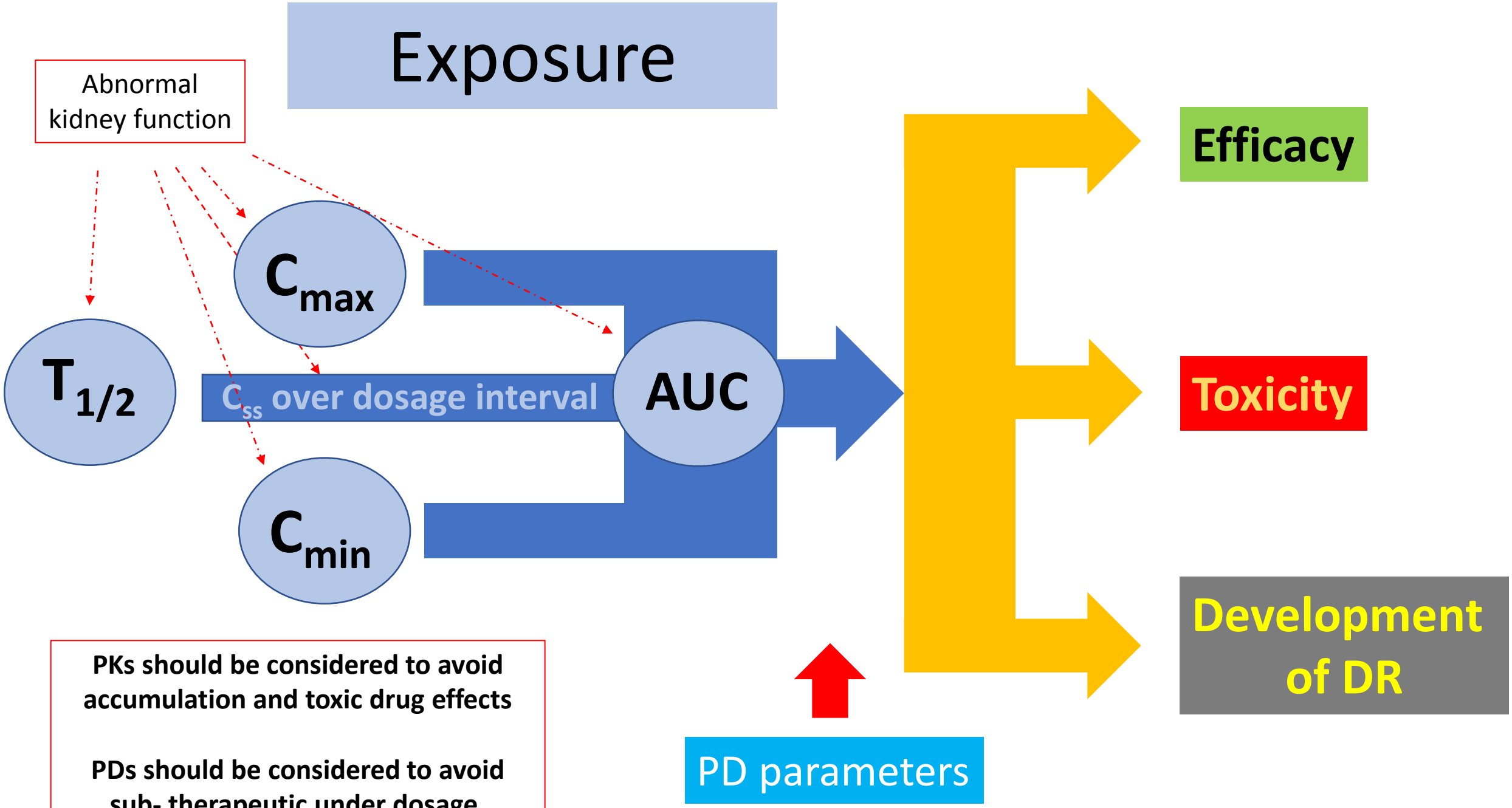
Facts related to estimation of GFR in patients with AKI

- No estimating equations can provide an accurate estimate of GFR in AKI since any endogenous filtration marker, such as creatinine, needs to be measured at steady state before it can provide a reliable estimate of GFR.
- It is near impossible to provide the best dosage regimen for AKI esp. with MOF/MODS patients because of their fluctuating kidney function, volume status, and potentially metabolic activity.

Antibiotic killing mechanisms

- Time- dependent killing : T> MIC
- Concentration- depending killing: Peak or AIU/ MIC


Exposure
C_{max}
$T_{1/2}$
C_{ss} over dosage interval
AUC
C_{min}
Efficacy
Toxicity
Development of DR
PD parameters
PD index:
T> MIC
Peak/ MIC
AUC/ MIC


Exposure
Abnormal kidney function
C_{max}
$T_{1/2}$
C_{ss} over dosage interval
AUC
C_{min}
Efficacy
Toxicity
Development of DR
PD parameters
PKs should be considered to avoid accumulation and toxic drug effects
PDs should be considered to avoid sub- therapeutic under dosage.

Antibiotic administration in patients with abnormal renal function

- Ehrlich: “frapper vite et frapper fort” >>> “hit fast, hit hard”.
- Tarragona strategy: the antibiotic regimen should be started fast and with a loading dose, whereas the dose adjustment follows the course and clinical condition.
- The immediate and high loading dose is very important >>> **It is a big mistake to adjust the dose to the impaired kidney function but to give no loading dose**

Initial reduction of CrCl produce relatively small change in $T_{1/2}$

Ehrlich P. Lancet 1913; 2: 353-9.
Sandiumenge A, et al. Intensive Care Med 2003; 29: 876-83.
Harbarth S, et al. Am J Med 2003; 115: 529-35.
Kumar A, et al. Chest 2009; 136: 1237-48.

Antibiotics dosing in patients with abnormal kidney function : How to do that?

- Loading dose : is **a "must" regardless of CrCl, i.e. critically ill**
- Maintenance dose : **to "achieve"** steady state blood concentrations
- Therapeutic drug monitoring: **"performed" at steady state**

Dose adjust, interval change, or both
: **during maintenance phase; clinically stable, stable estimated GFR**

Levey AS, et al. Ann Intern Med 2009; 150: 604–12.
Stevens LA, et al. Am J Kidney Dis 2010; 56: 486–95.

Antibiotics dosing in patients with abnormal kidney function : Loading dose

- Suitable for hydrophilic antibiotics (β-lactams, cephalosporins, and carbapenems) with long $T_{1/2}$
- The administration of loading doses (Max. therapeutic dose) are highly recommended.
- The immediate and high blood level is the target

Ulldemolins M, et al. Crit Care 2014; 18: 227

Antibiotics dosing in patients with abnormal kidney function : Maintenance dose

- To ensure steady- stage blood concentrations and lessen likelihood of sub-therapeutic concentrations
- In critically ill patients with AKI, a reduced maintenance dose is usually not needed before day- 3 of treatment (stable GFR)

Ulldemolins M, et al. Crit Care 2014; 18: 227.

Antibiotics dose- adjustment in patients with abnormal kidney function

Antibiotic	Action	Remark
β- lactam antibiotics	Either dose-adjusted or interval-adjusted or both	
Aminoglycosides	Keep the same dose, and interval-adjusted	50% of the standard high bolus loading dose , TDM
FQs	Keep the same dose, and interval-adjusted	-Except moxifloxacin -Monitoring of the QT interval
Cotrimoxazole	Dose- adjusted, and keep interval	
Glycopeptides, e.g. vancomycin	keep the same dose, and interval-adjusted	TDM

Manian FA, et al. Rev Infect Dis 1990. 12: 236–49.
Eyler RF, Mueller BA:. Adv Chronic Kidney Dis. 2010; 17: 392–403.
Eschenauer GA et al. Semin Dial 2016, 29: 204–13.
Gilbert B, et al. Med Clin North Am.2011; 95: 677–702, vii.
Lode H, et al. Clin Infect Dis. 1998; 27: 33–9.
Bennett WM, et al. Am J Kidney Dis. 1983; 3: 155–93.
Siber GR Jr., et al. Rev Infect Dis. 1982; 4: 566–78.

Antibiotics dosing in patients with abnormal kidney function : Therapeutic drug monitoring

The most effective dosing optimization strategy

- Peak level : IV >>> 30 min. after admin.
  : Oral >>> 60-120 min. after ingest
  : reflect maximum level achieved after rapid distribution and before elimination

- Trough level: just before the next dose: reflect the total body clearance

- Antibiotics that can be measured: **Amikacin, gentamicin, tobramycin, teicoplanin, vancomycin, colistin, piperacillin, meropenem and linezolid**

Ulldemolins M, et al. Crit Care 2014; 18: 227

Antibiotics “NOT” require any dose adjustment in renal failure

- Cloxacillin
- Doxycycline
- Linezolid
- Clindamycin
- Amphotericin
- Azithromycin
- Ceftriaxone
- Voriconazole

Antibiotics dosing in patients with abnormal kidney function : Under renal replacement therapy

- The risk of (insufficient) under dosage is higher than the risk of toxic overdose.

- For patients treated with intermittent hemodialysis, antibiotics should be given **after dialysis** to maintain effective drug levels in between each hemodialysis session

Janus N, et al. Ann Oncol 2010; 21: 1395-403.
Matzke GR, Comstock T.. In: Evans W, Schentag J, Burton M (eds). Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring, 4th edn. Lippincott, Williams & Wilkens: Baltimore, MD, 2005, pp 187–212.
Murphy JE. Clinical Pharmacokinetics Pocket Reference, 4th edn. American Society of Health-System Pharmacists: Bethesda, MD, 2008.

Antibiotics dosing in patients with abnormal kidney function : Under renal replacement therapy

- The dose after dialysis corresponds to the normal loading dose in most cases (or dose adjusted to kidney failure + supplement dose***)
- Antibiotics with small V_d, (< 1 L/kg), low molecular weight, water soluble, low protein binding >>> likely to be removed by HD ; usually require post HD **added dose**
- **During CRRT usually a normal or near normal dose is advisable.**

Janus N, et al. Ann Oncol 2010; 21: 1395-403.
Matzke GR, Comstock T.. In: Evans W, Schentag J, Burton M (eds). Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring, 4th edn. Lippincott, Williams & Wilkens: Baltimore, MD, 2005, pp 187–212.
Murphy JE. Clinical Pharmacokinetics Pocket Reference, 4th edn. American Society of Health-System Pharmacists: Bethesda, MD, 2008.

Tips

- In acute critically ill septic patients, on “the 1st. 24- h”, antibiotics “must” be started and continued with “therapeutic dose” (after loading dose) regardless of RRT initiation time.

- In patients with CRRT, the kinetic GFR is supposed to be ~ 30-60 mL/min, thus for most antibiotics, near normal dose & interval are efficacious and safe.

- **If TDM is not available, monitoring of potential toxicity is useful**

"When consulting the literature for dosing recommendations, it is important to select more recent studies utilizing similar dialysis technologies, as pharmacodynamic optimization strategies and dialysis technologies continue to evolve."

Eyler RF, Shvets K. CJASN. 2019; 14: 1080–90.

Resources for Dose Adjustments in CKD

Handbooks
Drug Prescribing in Renal Failure: Dosing Guidelines for Adults[1]
The Sanford Guide to Antimicrobial Therapy[2]
Mobile Application
Johns Hopkins Antibiotic Guide[3]
Online Subscriptions
AHFS Clinical Drug Information[4]
Micromedex[5]
Lexicomp[6]

References

1. Aronoff GRB, William M, Berns JS, Brier ME, Kasbekar N, Mueller BA, Pasko DA, Smoyer WE: *Drug prescribing in renal failure, 5th edition,* American College of Physicians, Philadelphia, PA, 2007
2. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, Pavia AT (Ed): *The Sanford Guide to Antimicrobial Therapy 2018, 48th edition,* Antimicrobial Therapy, Inc., Sperryville, VA,2018
3. Auwaerter PG (Ed.): *The Johns Hopkins POC-IT ABX Guide,* The Johns Hopkins University, Baltimore, MD, Available at: https://www.hopkinsguides.com/hopkins
4. McEvoy GK (Ed.): *AHFS Clinical Drug Information,* American Society of Health-System Pharmacists, Bethesda, MD, 2018
5. Micromedex Solutions. Truven Health Analytics, Inc, Ann Arbor, MI, Available at: http://www.micromedexsolutions.com
6. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL Accessed at: http://online.lexi.com

An ICU pharmacist >>> to prevent medication-related problems and enhance safe and effective medication use

Thank You for Your Attention